REMARKS

Claims 1, 3 and 7-50 were pending in the present application. Claims 11-12 and 19-50 were previously withdrawn from consideration. Claims 2 and 4-6 were previously canceled. Claims 1, 8 and 9 have been amended herein. Claim 7 has been canceled herein. Support for the amendments may be found throughout the specification and claims as originally filed. No new matter has been added.

Amendment or cancellation of claims should not be construed as an acquiescence, narrowing, or surrender of any subject matter. The amendments are being made not only to point out with particularity and to claim the present invention, but also to expedite prosecution of the present application. Applicants reserve the right to prosecute the originally filed claims further, or similar ones, in the instant or subsequently filed patent applications.

Rejection under 35 U.S.C. § 112, First Paragraph

The Examiner has rejected claims 1, 3, 7-10 and 13-18 under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. Specifically, the Examiner states that "[t]he instant claims encompass an MHC class II compound comprising any spaceholder molecule of any sequence that binds with intermediate or low affinity within the peptide binding groove and hinders the binding of any other peptide within the peptide binding groove, and not necessarily a CLIP peptide or substitution variant thereof capable of binding in the peptide binding groove, and including the spaceholder molecule that has, *i.e.*, comprises, the poly-Ala peptide recited in instant claim 10. There is insufficient disclosure in the specification on such a compound."

Applicants respectfully traverse the rejection. However, in an effort to expedite prosecution, Applicants have amended claim 1 to recite spaceholder molecules that are peptides. Applicants submit that a skilled artisan in the field would readily understand the metes and bounds of the claimed peptides based on the specification as filed. For example, Applicants disclose representative examples of the claimed peptides including SEQ ID NOs: 1-5, 8 and 36, as well as specific, non-limiting examples of binding affinities for these spaceholder molecules (see, for example, Example 1B). Applicants also submit that SEQ ID NOs: 1 and 8 have a common structure as CLIP peptides and that SEQ ID NOs:2-5 and 36 have a common structure as poly-alanine peptides. It is therefore Applicants' position that the specification provides

sufficient defining characteristics of the claimed genus of spaceholder peptides. In support of this view, Applicants point the Examiner to page 7 of the instant Office Action, in which the Examiner, in an attempt to formulate a *prima facie* obviousness case, points out that "DiBrino *et al* teach making poly-Ala peptides having residues deemed important for binding to an MHC molecule as well as performing an Ala scan on a peptide to study the contribution of each said residue for binding (especially Table III and column 2 on page 32429). Thus, based on the level of skill in the art, the specification and the available literature, one so skilled would understand the meets and bounds of the claimed invention.

Based at least on the foregoing, Applicants respectfully request reconsideration and withdrawal of the rejection.

Objections To Priority

The Examiner has deemed the filing date of the instant claims 8 and 9 to be July 11, 2003, which is the filing date of the instant application, because the parent provisional applications allegedly do not support the claimed recitations of "wherein said peptide is about 12-15 amino acid residues" and "wherein said peptide is about 13 amino acid residues."

Under the *Written Description Guidelines*, the requirement may be met for a claimed genus by the disclosure of a sufficient description of a representative number of species. Applicants submit that both parent provisional application 60/395,494, filed July 12, 2002 and 60/397,893, filed July 22, 2002, teach that "[e]xamples of spaceholder molecules include, but are not limited to, PVSKMRMATPLLMQA (SEQ ID NO:1); AAMAAAAAAAMA (SEQ ID NO:2); AAMAAAAAAAAAA (SEQ ID NO:3) AAFAAAAAAAAAA (SEQ ID NO:4); and ASMSAASAASMAA (SEQ ID NO:5)." (see page 4 and the claims of both 60/395,494 and 60,397,893). Since SEQ ID NO:2 comprises 12 amino acid residues, SEQ ID NO:1 comprises 15 amino acid residues, and SEQ ID NOs:3-5 each comprises 13 amino acid residues, Applicants submit that both parent provisional applications teach a representative number of species to inform a skilled artisan that Applicants were in possession of the claimed invention at the time the application was filed, as required by section 112, first paragraph.

Accordingly, Applicants respectfully request reconsideration and withdrawal of the objection and consideration of July 12, 2002 as the priority date for claims 8 and 9.

Rejections under 35 U.S.C. § 103(a)

The Examiner has rejected claims 1, 3, 7-9, 14 and 16-18 under 35 U.S.C. § 103(a) as being unpatentable over Zhong *et al.* (J. Exp. Med. 1996, 184: 2061-2066, of record) in view of Kozono *et al.* (Nature 1994, 369: 151-154, of record) and Natarajan *et al.* (J. Immunol. 1999, 162:4030-4036). Specifically, the Examiner states that "[i]t would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have produced the construct taught by Zhong *et al*, but with a processable linker such as taught by Kozono *et al* for their class II MHC/peptide molecule and optionally, to have made another such molecule comprising a low affinity peptide such as taught by Natarajan *et al* instead of the CLIP peptide taught by Zhong *et al*, and each molecule including a detectable label."

Applicants respectfully traverse the rejection. In order to establish a *prima facie* case of obviousness, the Examiner must determine the scope and content of the prior art, ascertain the differences between the claimed invention and the prior art and resolve the level of ordinary skill in the pertinent art. *Graham v. John Deere Co.*, 383 U.S. 1, 148 (1966). Once the Graham factual inquiries have been resolved, the Examiner must explain why the differences between the cited references and the claims would have been obvious to one of ordinary skill in the art. Fed. Reg. Vol. 72, No. 195, p. 57527. The Supreme Court in *KSR* stressed that "obviousness cannot be sustained by mere conclusory statements; instead there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *KSR* 127 S.Ct. 1727, 1740 (2007); see also Fed. Reg. Vol. 72, No. 195, p. 57529. "The key to supporting any rejection under 35 U.S.C. 103 is the clear articulation of the reason(s) why the claimed invention would have been obvious." Fed. Reg. Vol. 72, No. 195 at p. 57528.

Applicants respectfully remind the Examiner that each reference must be considered in its entirety, for all that it teaches. Thus, references must be viewed as a whole and must suggest the desirability of the claimed invention without the benefit of impermissible hindsight reconstruction afforded by the claimed invention. Under *KSR*, "teaching away" still provides evidence of non-obviousness. *See* 127 S.Ct. at 1745. "[P]roceeding contrary to accepted wisdom in the art is evidence of nonobviousness." M.P.E.P. §2145 (citing *in re Hedges*, 783 F.2d 1083 (Fed. Cir. 1986)). If when combined, the references "would produce a seemingly inoperative device," then they teach away from their combination. *Tec Air, Inc. v. Denso Mfg. Michigan, Inc.*, 192 F.3d 1353, 1360 (Fed. Cir. 1999). *See also, In re Fritch*, 972 F. 2d 1260,

1265 n. 12 (Fed. Cir. 1982) ("A proposed modification [is] inappropriate for an obviousness inquiry when the modification render[s] the prior art reference inoperable for its intended purpose.").

According to the Examiner, Zhong *et al.* discloses MHC class II compounds comprising the MHC class II α chain and the MHC class II β chain, the β chain covalently linked to the mouse Ii 89-100 invariant chain CLIP peptide or high affinity antigenic spaceholder molecules (*e.g.*, peptides) via a linker, wherein the compound is further associated with a chemical dye on SDS-PAGE or associated with a radiolabel upon metabolic labeling. Zhong *et al.* does not teach or suggest the use of a spaceholder molecule, wherein said spaceholder molecule is linked to the claimed MHC class II by a processable linker as claimed in amended claim 1 and dependent claims thereof. Contrary to the claimed invention, in which the removal of spaceholder molecules (e.g., peptides) that bind the claimed MHC class II molecules with low or intermediate affinity is mediated by a processable linker, Zhong *et al.* teaches away because they use a ***covalently linked, non-processable linker that would enhance rather than reduce peptide binding*** stating that:

> [t]o examine whether groove binding could substitute for Ii in promoting class II ER to Golgi complex trafficking, ***it was necessary to attain near stoichiometric occupancy*** of newly synthesized class II dimers with CLIP or alternative ligands. We first determined if this could be accomplished by biosynthetic attachment of peptide sequences to the NH_2 terminus of the β chain (see page 2062, right column, first paragraph) (Emphasis added).

According to the Examiner, Kozono *et al.* discloses an MHC class II compound comprising the extracellular domains of the α and β chains of MHC class II, and a peptide attached by a flexible peptide linker to the amino terminus of the MHC class II β chain and including a thrombin sensitive cleavage site, wherein the peptide is a ***13-mer peptide that binds well*** to the binding groove formed by the MHC class II chains, said compound being immobilized by an anti-β chain monoclonal antibody or absorbed to tissue culture plate wells, *i.e.*, the MHC class II component is linked to the effector component. Kozono *et al.* does not teach or suggest the use of a spaceholder molecule, wherein said spaceholder molecule binds with intermediate or low affinity as claimed in amended claim 1 and dependent claims thereof. Contrary to the claimed invention in which spaceholder molecules (*e.g.*, peptides) bind the claimed MHC class II molecules with low or intermediate affinity, Kozono *et al.* teaches away

from the claimed invention because Kozono *et al.* specifically discloses ***spaceholder molecules (e.g., peptides) that bind MHC class II molecules with high affinity*** stating that:

> MHC proteins are associated with many different self peptides, making it impossible to know which self peptide was involved in positive or negative interactions with a particular T cell. These studies as well as *in vitro* studies on TCR-peptide-MHC interactions would be aided by a means of producing MHC molecules containing a single peptide…We selected spaceholder molecules (e.g., peptides) known to ***bind well*** to the clefts of these class II molecules (see the abstract and page 151, right column, first paragraph) (Emphasis added).

Natarajan *et al.* teaches incubating insect cell-produced class II molecules with low affinity peptide(s). Natarajan *et al.* does not teach or suggest the use of a spaceholder molecule, wherein said spaceholder molecule is linked to the claimed MHC class II by a processable linker as claimed in amended claim 1 and dependent claims thereof. Contrary to the claimed invention in which the removal of spaceholder molecules (*e.g.*, peptides) that bind the claimed MHC class II molecules with low or intermediate affinity can be accomplished at a defined timepoint through the use of a processable linker, Natarajan *et al.* teaches away from the claimed invention because Natarajan *et al.* specifically discloses the use of a ***peptide lacking a processable linker spaceholder molecule*** in order to allow random dissociation from the MHC class II, which is a prerequisite for kinetic analyses stating that:

> [w]e used dissociation of short-lived complexes with low affinity peptides to generate nascent DR1 molecules in correct conformations. A new fluorescence assay that enables simultaneous detection of two different peptide complexes indicates that this nascent molecule forms a stable complex with the high affinity HA peptide at the same rate at which it is generated. ***Rigorous kinetic analyses*** indicate that the stable peptide binding reaction has to be extremely rapid to result in single exponential kinetic rates similar to the dissociation rate of the short-lived complex, and might even be ***spontaneous*** (see page 4033, right column, first paragraph of the Discussion section) (Emphasis added).

Contrary to the Examiner's assertion that it would have been *prima facie* obvious for a skilled artisan to produce the construct taught by Zhong *et al.* but with a processable linker such as taught by Kozono *et al.*, Applicants submit that Zhong *et al.* specifically discloses the use of a covalently linked, non-processable linker that would ***enhance*** peptide binding for the reasons stated above and that this teaches away from a processable linker whose purpose is to ***facilitate removal*** of spaceholder molecules (*e.g.*, peptides) that bind MHC class II molecules with low or intermediate affinity, as claimed. In addition, Applicants submit that it would also not have been

prima facie obvious for a skilled artisan to produce the construct taught by Kozono *et al.* but with spaceholder molecules (*e.g.*, peptides) that bind MHC class II molecules with low or intermediate affinity as taught by Zhong *et al.*, because Kozono *et al.* specifically discloses spaceholder molecules (*e.g.*, peptides) that bound MHC class II molecules with ***high affinity*** for the reasons stated above and that this teaches away from the use of spaceholder molecules (e.g., peptides) that bind MHC class II molecules with ***low or intermediate affinity*** whose purpose is to facilitate the removal of spaceholder molecules, as claimed. The combination of Zhong *et al.* or Kozono *et al.* with Natarajan *et al.*, does not remedy these deficiencies because Natarajan *et al.* does not teach or suggest, and actually teaches away from, the use of a spaceholder linked to the claimed MHC class II by a processable linker, for the reasons stated above.

Based at least on the foregoing, Applicants respectfully request reconsideration and withdrawal of the rejection.

The Examiner has also rejected claims 10-12 under 35 U.S.C. § 103(a) as being unpatentable over Zhong *et al.* (J. Exp. Med. 1996, 184: 2061-2066, of record) in view of Kozono *et al.* (Nature 1994, 369: 151-154, of record) and Natarajan *et al.* (J. Immunol. 1999, 162:4030-4036) as applied to claims 1, 3, 7-9, 14 and 16-18 above, and further in view of Malcherek *et al.* (J. Exp. Med. 1995, 181: 527-436, IDS reference) and DiBrino *et al.* (J. Biol. Chem. 1994, 269(51): 32426-32434, of record). Specifically, the Examiner states that "[i]t would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have extended the amino terminus of the CLIP 105-117 peptide out sequentially (as well as the carboxy terminus), including making a peptide with the sequence PVSKMRMATPLLMQA (amino acid residues 103-117), in order to determine if binding fully commensurate with the CLIP 97-120 peptide could be obtained, and to have made a construct of the structure taught by the combined references, but using a human HLA class II molecule such as HLA-DR17 taught by Malcherek *et al.* that binds the CLIP 105-117 and the CLIP 97-120 peptide, and the extended peptides such as CLIP 103-117."

Applicants respectfully traverse the rejection. Claims 10-12 are dependent upon claim 1. The Examiner relies on the combination of Zhong *et al.*, Kozono *et al.*, and Natarajan *et al.* for presenting a *prima facie* case of obviousness regarding claims 1, 3, 7-9, 14 and 16-18. For the reasons stated above, Applicants submit that the Examiner has failed to present a *prima facie*

case of obviousness based on the combination of Zhong *et al.*, Kozono *et al.*, and Natarajan *et al.* Furthermore, the Examiner admits that the combination of Zhong *et al.*, Kozono *et al.*, and Natarajan *et al.* "do[es] not teach wherein the CLIP peptide is PVSKMRMATPLLMQA, AAMAAAAAAAMA, AAFAAAAAAAAAA, or AAMAAAAAAAAAA" (see pending Office Action, page 6).

Malcherek *et al.* discloses human CLIP peptides having residues deemed important for binding to an MHC molecule and an alanine-based peptide scan for studying the contribution of each residue of said human CLIP peptides for binding to an MHC molecule. DiBrino *et al.* discloses poly-alanine peptides having residues deemed important for binding to an MHC molecule and an alanine-based peptide scan for studying the contribution of each residue of a peptide for binding to an MHC molecule. Applicants submit that the disclosure of human CLIP and alanine-based peptides by Malcherek *et al.* and DiBrino *et al.*, respectively, does not remedy the deficiencies of Zhong *et al.*, Kozono *et al.*, and Natarajan *et al.* for failing to teach or suggest all of the elements of claim 1, as stated above, from which claims 10-12 depend. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection.

The Examiner has also rejected claims 13-15 under 35 U.S.C. § 103(a) as being unpatentable over Zhong *et al.* (J. Exp. Med. 1996, 184: 2061-2066, of record) in view of Kozono *et al.* (Nature 1994, 369: 151-154, of record) and Natarajan *et al.* (J. Immunol. 1999, 162:4030-4036) as applied to claims 1, 3, 7-9, 14 and 16-18 above, and further in view of Crawford *et al.* (Immunity. 1998, 8: 675-682, IDS reference). Specifically, the Examiner states that "[i]t would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have multimerized the complexes taught by the combined references, plus or minus the leucine zipper peptides, using the methodology of Crawford *et al.*"

Applicants respectfully traverse the rejection. Claims 13-15 are dependent upon claim 1. The Examiner relies on the combination of Zhong *et al.*, Kozono *et al.*, and Natarajan *et al.* for presenting a *prima facie* case of obviousness regarding claims 1, 3, 7-9, 14 and 16-18. For the reasons stated above, Applicants submit that the Examiner has failed to present a *prima facie* case of obviousness based on the combination of Zhong *et al.*, Kozono *et al.*, and Natarajan *et al.* Furthermore, the Examiner admits that the combination of Zhong *et al.*, Kozono *et al.*, and

Natarajan *et al.* "do[es] not teach wherein the effector component is biotin" (see pending Office Action, page 8).

Crawford *et al.* teaches multimerization of MHC class II/peptide complexes by including a peptide tag capable of being biotinylated, biotinylating the MHC complexes, and mixing the MHC class II/peptide complexes with phycoerythrin/strepatividin. Crawford *et al.* does not teach or suggest the use of a spaceholder molecule, wherein said spaceholder molecule is linked to the claimed MHC class II by a processable linker and binds the claimed MHC class II molecules with low or intermediate affinity. Moreover, Crawford *et al.* teaches away from the claimed invention, because Crawford *et al.* teaches a ***covalently linked, non-processable linker and spaceholder molecules (e.g., peptides) that bind MHC class II molecules with high affinity*** stating that:

> we combined the use of soluble multivalent MHC class II molecules with a method that ***assures complete stable occupancy of the MHC binding groove*** with a single peptide by ***genetically attaching*** the peptide to the MHC molecule with a flexible linker. (see page 675, right column, last paragraph of the Introduction section) (Emphasis added).

The single peptides used by Crawford *et al.* include moth cytochrome c and chicken ovalbumin peptides known to bind MHC class II molecules with high affinity (see Kozono *et al.* pg. 151 and Crawford *et al.* pg. 680, of record). Applicants submit that the disclosure of multimerized MHC class II/peptide complexes using a peptide tag capable of being biotinylated as taught by Crawford *et al.* does not remedy the deficiencies of Zhong *et al.*, Kozono *et al.*, and Natarajan *et al.* for failing to teach or suggest all of the elements of claim 1, as stated above, from which claims 13-15 depend. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection.

CONCLUSION

In view of the foregoing remarks, Applicants submit that the pending claims are in condition for allowance. Early and favorable reconsideration is respectfully solicited. The Examiner may address any questions raised by this submission to the undersigned at (617) 832-1000. If any fees are due, the Commissioner is hereby authorized to credit any overpayment or charge any deficiencies to Deposit Account No. **Deposit Account No. 06-1448, Reference No. DFS-044.01.**

Respectfully submitted,

Foley Hoag LLP

Dated: March 26, 2008
Customer No: 25181
Patent Department
Foley Hoag, LLP
155 Seaport Blvd.
Boston, MA 02210-2600

/Hathaway P. Russell/
Hathaway P. Russell, Esq.
Reg. No. 46,488
Attorney for Applicants